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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,256	10/02/2001	Naoyuki Fukuchi	214595US0PCT	8955

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OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
DESAI, ANAND U	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 01/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,256	FUKUCHI ET AL.	
	Examiner	Art Unit	
	Anand U. Desai, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *11-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 12/27/2001; 2/21/2002; 3/10/2003; 5/2/2003
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, drawn to a method of producing a subunit peptide, claims 1-10, in the reply filed on October 17, 2005 is acknowledged. The traversal is on the ground(s) the special technical feature is improperly identified, the International Preliminary Examination Authority did not find unity of invention lacking, and that no burden exists for searching the entire application. This is not found persuasive because as stated in the examination of method claims 1-10, and composition claims 11-15 would impose a search burden. If as Applicants' states the special technical feature of a "subunit peptide originating from an oligomeric protein having disulfide bonds within a subunit and between subunits, and a polyoxyalkyl polyether bonded to a cysteine residue" is the correct special technical feature, then the special technical feature still does not define a contribution over the prior art, because Shadle et al. (U.S. Patent 4,847,325) disclose the method of conjugating a polyethylene glycol with a cysteine residue from colony stimulating factor-1 (see entire document, particularly col. 6, lines 46, 47, col. 11, line 67, claims 1, 8, and 18). The requirement is still deemed proper and is therefore made FINAL.

2. Claims 11-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 17, 2005.

Priority

3. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The priority date is April 2, 1999.

Information Disclosure Statement

4. The information disclosure statements (IDSs) submitted on December 27, 2001, February 21, 2002, March 10, 2003, and May 2, 2003 are being considered by the examiner. Reference AA is being crossed out of the March 10, 2003 IDS, because it is listed on the February 21, 2002 IDS form as reference AA. Reference AP is being crossed out of the May 02, 2003 IDS, because it is listed on the February 21, 2002 IDS form as reference AU. References AO through AS are being crossed out of the December 27, 2001 IDS, because they are listed on the February 21, 2002 IDS form as references AO through AS.

Specification

5. The disclosure is objected to because of the following informalities:

6. A reference is missing from the first line of the specification to prior filled applications. Suggested updating the continuity data on line 1 of the specification.

7. The brief descriptions of the drawings do not describe the individual figures. The figures have multiple sections that are not labeled individually.

8. The drawing (Figure 6) sets forth peptide sequences (peptide numbers: 2-6 in Figure 6) without reciting the corresponding sequence identifiers (SEQ ID NO: _). Applicant is required to comply with requirements for patent application containing amino acid sequence disclosure.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. In claim 1, step (b) is the subunit peptide bonded to the polyoxyalkyl polyether through the thiol group? Does the subunit peptide comprise the thiol group?

12. In claim 1, the end result appears to be purifying rather than of producing a subunit peptide?

13. In claim 9, it is unclear if the polyoxyalkyl polyether is bonded to cysteine residues that are involved in intermolecular or intramolecular or both interactions? Is it in the alternative, if so is the word, "or" missing before the word "among"?

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1-7, and 10 are rejected under rejected under 35 U.S.C. 103(a) as being unpatentable over Woghiren et al. (Bioconjugate Chem. 4: 314-318 (1993)) in view of Shadle et al. (U.S. Patent 4,847,325).

Woghiren et al. disclose the conjugation of modified monomethoxypolyethylene glycol (average molecular weight 5000 Da) with cysteine residues in proteins. Woghiren et al. describe the transformation of monomethoxypolyethylene glycol into a reactive intermediate composed of a thiol protected polyethylene glycol using 4,4'-dipyridyl disulfide (see page 315, scheme 1). Woghiren et al. describe the formation of polyethylene glycol-BPTI (Bovine Pancreatic Trypsin Inhibitor). The conjugation of modified polyethylene glycol with BPTI is conducted with a free sulfhydryl group reduced form of BPTI, and a non-reduced form of BPTI to monitor the formation of conjugate. The conjugation was carried out in five separate reaction buffers of varying pH from 2.7 to 10 (see Experimental Procedures, Formation of polyethylene glycol-BPTI at varying pH). The results demonstrate the formation of conjugate only with the BPTI containing a free sulfhydryl group at varying pH. "No reaction was observed in the control unreduced BPTI..." (see page 317, right hand column below figure 4). Woghiren et al. does disclose the method of conjugating a polyethylene glycol to a cysteine residue in a protein. Woghiren et al. does not disclose the conjugation of polyethylene glycol with a subunit peptide originating from an oligomeric protein.

Shadle et al. disclose the conjugation of water-soluble polymers selected from the group consisting of polyethylene or polypropylene glycol homopolymers, polyoxyethylated polyols, and polyvinyl alcohol with human colony stimulating factor-1 (CSF-1), (see claim 1). The modified CSF-1 retains "useful biological activity" (see col. 4, line17). "The CSF-1 employed herein may be the native dimer or recombinantly produced dimer" (see col. 6, lines 47-49). Shadle et al. disclose engineering of cysteine residues into CSF-1 to create a recombinant CSF-1 with a free sulfhydryl group for a PEG reaction (see col. 9, lines 14-18). Shadle et al. disclose

"the object of the modification is to obtain a conjugated protein with retained biological activity, ...and with reduced immunogenicity" (see col. 12, line 47-52). Shadle et al. disclose the refolding of endogenous sulfhydryl groups to disulfides that establish the biologically active dimeric configuration of CSF-1 (see col. 10, lines 57-62). Shadle et al. disclose the conjugation of a recombinant heterodimer consisting of one subunit containing a cysteine residue with a free sulfhydryl group reactive with the polymer (see claim 8). Shadle et al. disclose the conjugation of a polymer that contains a maleimido group that reacts with the free sulfhydryl group of the cysteine residue (see claim 18).

A person having ordinary skill in the art would have been motivated to conjugate a polyethylene glycol polymer disclosed by Woghiren et al. with the cysteine residues of CSF-1, because of the enhanced pharmacological properties of the conjugate, such as increased half-life, and reduced immunogenicity. One would have expected to succeed in producing the conjugate because Shadle et al. has disclosed the conjugation of cysteine containing CSF-1 with polyethylene glycol. Therefore, it would have been obvious to the person having ordinary skill in the art to produce a polyethylene glycol conjugated subunit peptide by exposing the free sulfhydryl containing subunit peptide with an activated polyethylene glycol polymer.

16. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Woghiren et al. (Bioconjugate Chem. 4: 314-318 (1993)) in view of Shadle et al. (U.S. Patent 4,847,325) as applied to claims 1-7 above, and further in view of Deng et al. (Biochem Biophy Res Commun 228(2):557-566 (1996)).

Woghiren et al. and Shadle et al. are discussed above. Neither reference explicitly states the inhibition of physiological activity upon the binding of polyoxyalkyl polyether polymer to a subunit peptide.

Deng et al. disclose the inhibition of CSF-1 physiological function such as dimer formation and cell surface expression when cysteine 102 and 146 are substituted. Therefore, it would have been obvious to the person having ordinary skill in the art to inhibit the physiological function of a CSF-1 peptide by preventing an intramolecular disulfide bond through the conjugation of a polyoxyalkyl polyether polymer to either cysteine 102 or 146 of CSF-1.

Conclusion

17. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U. Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 7:00 a.m. - 3:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (517) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

January 3, 2006

JON WEBER
SUPERVISORY PATENT EXAMINER